Use of Biosimilars in Pediatric Inflammatory Bowel Disease: An Updated Position Statement of the Pediatric IBD Porto Group of ESPGHAN

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ABSTRACT

Biologic therapies have changed the outcome of both adult and pediatric patients with Inflammatory Bowel Disease (IBD). In September 2013, the first biosimilar of infliximab was introduced into the pharmaceutical market. In 2015, a first position paper on the use of biosimilars in pediatric IBD was published by the ESPGHAN IBD Porto group. Since then, more data have accumulated for both adults and children demonstrating biosimilars are an effective and safe alternative to the originator. In this updated position statement, we summarize current evidence and provide joint consensus statements regarding the recommended practice of biosimilar use in children with IBD.

Key Words: biologics, biologics, biosimilars, biosimilars, Crohn disease, inflammatory bowel disease, pediatric, ulcerative colitis

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What Is Known

- Before approval of a biosimilar, similarity needs to be proven, instead of efficacy and safety.
- Introduction of biosimilars to the market leads to substantial cost reduction.

What Is New

- A switch from the originator infliximab to CT-P13 may be considered in children with IBD in clinical remission, following at least 3 induction infusions.
- Multiple switches (>1 switch) between biosimilars and reference drug or various biosimilars are not recommended in children with IBD, as data on interchangeability is limited and traceability of the drugs in case of loss of efficacy and/or safety signals may be compromised.
- Physicians/institutions should keep records of brands and batch numbers of all biological medicines (including biosimilars) administered.

Anti-tumor necrosis factor alpha (TNFα) agents including infliximab (IFX) and adalimumab are monoclonal antibodies approved for the treatment of Crohn disease (CD) and ulcerative colitis (UC) in children as well as for other inflammatory indications. The patent for the IFX originator (Remicade; Janssen Biologics, The Netherlands) expired in 2015 in Europe while the first biosimilar (BioS) CT-P13 was approved by the European

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Medicines Agency (EMA) in 2013 and by the US Food and Drug Administration (FDA) in 2016. The access to TNFα inhibitors and the local policies regarding the use of these agents vary substantially between regions and countries. The aim of this position paper is to summarize the current evidence on the use of BioS in pediatric inflammatory bowel diseases (IBD) including efficacy, safety (immunogenicity), switching, interchangeability, cost effectiveness, and extrapolation from adult data.

Biosimilars Regulatory Processes

BioSs have been approved for use in Europe and Canada for about a decade following regulatory guidance that was developed in Europe in 2005 before the approval of BioS somatotropin in 2006. BioSs approved for patients with IBD are listed in Table 1. A BioS is defined by the FDA as a biological product that is highly similar to the reference product with respect to safety, purity and potency and by EMA as a biological medicinal product containing a version of the active substance of an already authorized original biological medicinal product.

Primarily, similarity needs to be proven, instead of efficacy and safety which has already been proven for the originator product. Minor differences are allowed in inactive components. Data to support a claim of biosimilarity can be analytic, based on animal data, and at least 1 pharmacokinetic/pharmacodynamic (PK/PD) study in humans. Demonstration of efficacy and safety in patients are not required for approval. If there is strong evidence that PK/PD data correlate well between the BioS and the reference product, comparative efficacy studies in patients may not be needed.

The regulatory process is a progression of 4 steps with each step intended to compare the BioS to the reference product (1,2): analytical studies in which the structural (eg, identical amino acid sequence) and functional characteristics (activity, potency) are compared to the reference product. Comparison of non-clinical assessments which for most BioS products involve non-human primates. Phase 1 PK/PD studies (usually involving single-dose in vivo comparative studies) including half-life and immunogenicity. Clinical trials in patients (a single phase 3 trial is usually sufficient). The decision for approval is based on the totality of evidence obtained in each of the 4 steps.

Extrapolation

Extrapolation is the process of approving a BioS for all of the approved indications of the originator drug, even if the BioS has not been formally studied in all the indications or populations of the originator product (3–5). In clinical practice, extrapolation of molecules in the same class sharing the same mechanism of action from adult to pediatric (6,7) or across indications (8,9) is common in case there are not enough data available or when clinical trials are ongoing. Extrapolation allows keeping the cost of BioS competitive with subsequent greater market availability (4,10,11). On the other hand, proven mechanism of action (eg, TNF blocking) in different diseases may not result in same clinical efficacy (9,12,13). Different modes of action may exist, depending on binding properties and receptor activation or blockade.

As IBD is a complex disease with differences between pediatric-onset and adult-onset disease, the decisions of regulatory agencies on extrapolation of indications to IBD were challenged by both adult (ECCO) and pediatric (ESPGHAN) gastroenterology societies (14,15). In 2014, Health Canada did not approve IFX BioS for IBD due to lack of clinical data, molecular glycosylation differences and uncertainty resulting from small differences in antibody-dependent cell-mediated cytotoxicity (9,10,16–18). However, in view of the emerging data, Health Canada has now recommended BioS IFX for all the indications of originator IFX by extrapolation (19).

In 2015, the Porto IBD working group of ESPGHAN published a position paper on the use of BioS in pediatric IBD (15). At that time, only very limited data from literature were available on clinical experience with BioS CT-P13 (20–24). Even though FDA and EMA accepted extrapolation to other indications, the Porto group concluded in 2015 that extrapolation to children with IBD should be done with caution as there were no data from RCTs available in IBD patients. Concerns on extrapolation were based on differences in dosage of IFX, antibody formation, type of concomitant immunosuppression between rheumatoid diseases and IBD and lack of pharmacodynamic markers (15). Moreover, studies were all performed in adult patients.

Performing RCTs with BioS in all extrapolated indications is very costly and time consuming, thus available evidence will mainly accumulate post-market, non-controlled, observational trials. Since BioS approval by regulatory agencies, a number of clinical data reports were published on BioS in both adult and paediatric IBD (10,25–33) but no major clinical trials have compared the efficacy of IFX originator and its BioS specifically in patients with IBD (10). The NOR-SWITCH RCT trial (34) found comparable safety and efficacy in patients with various diagnoses (including IBD) switching from IFX to CT-P13.

A study in 692 IBD patients including 112 children did not find any age-related differences in pharmacokinetics of originator IFX, but children of different weight and age groups were not compared separately (7,35).

Attention should also be given to perception by clinicians and patients who may be concerned by indication as well as population extrapolation of BioS (4,36–41). Such a perception may give rise to a so-called nocebo effect: a negative treatment experience induced by non-pharmacological negative expectations among patients. A more recent ECCO survey in 2016 showed a shift in opinion in favor of BioS (42).

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TABLE 1. European Medicines Agency approved biosimilars

Biosimilar product	Reference product	Indication	Date of approval	Manufacturer
Inflectra	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	September 10, 2013	Hospira
Remsima	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	September 10, 2013	Celltrion
Flixabi	Infliximab	Ankylosing spondylitis Crohn's disease Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis	May 26, 2016	Samsung Bioepis
Solymbic	Adalimumab	Ankylosing spondylitis Crohn's disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	March 22, 2017	Amgen
Amgevita	Adalimumab	Ankylosing spondylitis Crohn's disease Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis	March 22, 2017	Amgen
Imraldi	Adalimumab	Ankylosing spondylitis Arthritis Crohn's Disease Hidradenitis suppurativa Psoriatic arthritis, Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	August 24, 2017	Samsung Bioepis
Cyltezo	Adalimumab	Crohn's disease Hidradenitis suppurativa Juvenile idiopathic arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Uveitis	CHMP positive opinion 15 Sep 2017	Boehringer Ingelheim

Modified from http://www.gabionline.net/BSs/General/BSs-approved-in-Europe] (ordered by date of approval.

Transition, Switching, and Interchangeability

BioS approval by a regulatory agency does not imply that transition, switching, substitution or interchangeability has been assessed (see definitions in Table 2). Regulatory agencies usually do not demand switching studies in order to approve BioSs, with the exception of the FDA who requires a single transition evaluation and a study with 3 reference BioS switches to demonstrate interchangeability for products that claim this property (43). Until now, not a single product has been able to fulfil this interchangeability requirement so the FDA has not certified interchangeability yet for any product.

There is a considerable body of evidence that transition from reference IFX to CT-P13 is safe with minimal difference in efficacy and immunogenicity (44,45). However, clinical studies are of small numbers and of relatively short duration. There are currently limited data for SB2 (Flixabi/Renflexis) in IBD. At ECCO 2018 an abstract describing the clinical outcome and immunogenicity over 6 months after transitioning from Remicade to SB2 (Flixabi) in 119 adult IBD patients reported no effect on clinical outcome or immunogenicity (46). There is as yet (May 2018) no data on and any BioS adalimumab in IBD. Therefore, at present, transition is possible; however, it should be performed after a clinical decision made by the physician and

TABLE 2. Terms and definitions

Terms	Definition and clinical scenario
Transition	Change from one biologic to its alternative, for example, from a reference product to its BioS version.
Switching	In a wider sense: changing treatment A for treatment B, for example, from infliximab to adalimumab or vedolizumab. Confusingly also used to describe Replacing a reference product by its BioS alternative by a treating physician decision. However, this is continuing treatment with a variation of the same molecule, so not a real switch. Single-switch means crossover studies, when patients starting on the reference product are switched to its BioS and patients starting on the BioS are switched to the reference agent. Each patient experiences only one change in therapy. In studies with multiple-switch design, patients undergo a series of switches alternating between the reference product and its BioS alternative.
Interchangeability	FDA definition (USA): Between the reference product and its BioS means possibility to repeat switch from one to another with no greater safety or efficacy risk than continued use of the reference product. For an interchangeable biologic product, it means additional standards to produce the same clinical result when compared to the reference product and does not increase safety risk or diminish efficacy when switching from the originator drug. Currently, there are no data on interchangeability of IFX BioSs.
	In EU, EMA is assessing interchangeability on the population level, and does not assess its appropriateness on the level of an individual patient, which is left at the discretion of a healthcare professional. No guidance is here to be expected from EMA.
Substitution (automatic)	Is a practice at the pharmacy level of dispensing an equivalent product instead of a certain prescribed medicine, without consulting the prescribing physician. In Europe this practice is almost universally not allowed, with only a few exceptions. Automatic substitution in a hospital may be agreed on the level of the Drug & Therapeutics Committee.

on available scientific evidence with patient's awareness and acceptance.

Patients positive for anti-drug-antibodies (ADAs) are theoretically more likely to develop adverse reactions, therefore in patients who are durably positive for these antibodies, transition to BioS should proceed with caution with measurement of drug levels and antibodies post switching (47–49).

Switching between reference biologic and its BioS versions is primarily performed not for clinical but rather for economic and regulatory reasons (eg, creating a wider access for patients). As formal head to head comparison between different biosimilars has not been performed, interchangeability back and forth is not recommended although, based on immunogenicity studies, significant problems are not expected. It seems prudent that until further evidence is available, this practice should be performed under controlled circumstances where clear planned prospective analysis of outcomes is in place.

Update of Pediatric data Available

Despite the priority to perform pediatric trials, only a small number of prospective, observational studies have been published. In the first study, Sieczkowska et al included 39 children (32 with CD and 7 with UC), who were switched from the IFX originator to its BioS, prospectively, following induction (32). At the moment of switching, 69% patients were in clinical remission, and at the end of the follow-up period of 11 months, 88% had remained in clinical remission. The UC group was more heterogeneous as some patients were switched to IFX BioS during induction therapy, limiting the possibility of comparing originator and BioS in terms of their efficiency. Among the patients with UC, only 4 of 7 were still receiving BioS treatment at the end of follow-up, all of whom were in clinical remission.

The second study from Sieczkowska et al was a prospective induction study (50) which included 36 CD children (75% anti-TNF naïve), with luminal and/or perianal CD (n = 7) reporting a clinical response or remission at week 14 in 86% and 67% patients, respectively. A significant clinical improvement in fistula closure was observed as well. There was no difference in the rate of the response to BioS IFX among IFX naïve or IFX exposed patients. No statistical difference was found against reference IFX historical data.

In a prospective cohort of 40 pediatric CD patients Richmond et al (51) reported that CT-P13 was associated with a significant clinical and biochemical improvement post induction, with no significant safety issues noted.

In a recent prospective observational study (52), patients with pediatric-onset IBD receiving the originator IFX for 1 year were selected either to continue maintenance with the originator (36 patients) or to the CT-P13 switch group (38 patients). After 1 year 86.1% and 92.1% were on the drug, while 77.8% and 78.9% experienced persistent remission, respectively, with no difference in pharmacokinetics, immunogenicity or adverse events between the time of switch and 1-year post-switch.

Chanchlani et al, in a prospective audit of patients starting anti-TNF therapy (175 originator drug, 82 CT-P13), reported no difference in response to treatment between groups (53). Several additional reports published in abstract form (Table 3) support the above published trials.

These encouraging results are limited by the lack of endoscopic assessment. Moreover, most of the patients (n = 97 out of 115, 84%) on BioS IFX received concomitant immunosuppressant (32,50,51).

Currently, many European countries already switched fully to CT-P13 and the number is growing rapidly (Fig. 1A and B). As such, more data is expected to accumulate in the near future. There are no published pediatric trials using the second BioS of IFX SB2 (Flixabi) that received approval in May 2016.

In summary, in a total of 196 pediatric CD patients, response and remission rates were reported from 67% to 87%, respectively. In pediatric UC patients, response rates were lower and patient numbers are smaller (67 patients) with remission rates ranging from 36% to 87%. In severe acute colitis response was much less pronounced than in refractory colitis (36% vs 64%) but numbers are very low (4/11). Overall adverse event rates were comparable to the historic data on the originator IFX.

Adult Data Where Pediatric Data Are Lacking

Efficacy and Safety

In a large prospective multicenter cohort study (210 patients: 126 CD, 84 UC), induction with CT-P13 (26) resulted in significantly higher clinical remission rates in patients without previous exposure to the originator IFX compared with those previously exposed (60.9% vs 35.7% in CD and 65.1% vs 33.3% in UC). Another large prospective, Italian multicenter, cohort study in 313 CD and 234 UC consecutive patients treated with CT-P13 showed results in line with the IFX originator in term of efficacy and safety (54). A recent meta-analysis by Komaki et al analyzed all the available literature on the use of CT-P13 IFX BioS in adults with active IBD (55). Seven studies (4 prospective and 3 retrospective) including 552 patients showed that induction with CT-P13 yielded a high pooled rate of clinical response and remission with low rate of adverse events (8%) concluding that CT-P13 was associated with excellent clinical efficacy and safety profile.

There is only 1 published study to date using the IFX BioS SB2: a phase 3, randomized, double-blind, study in patients with moderate to severe rheumatoid arthritis (RA) showing that SB2 was

TABLE 3. Paediatric data on biosimilars (published papers and abstracts)

Study, Year (Reference, source)	Study design	Name of biosimilar	Indications and patients (n)	Phase and mean term of study (weeks)	Including switching
Sieczkowska et al. 2016 (32)	Prospective	CT-P13	CD-32, UC-7	Maintenance (35)	Yes
Sieczkowska et al. 2016 (50)	Prospective	CT-P13	CD-36	Induction (14)	No
Richmond et al. 2018 (51)	Prospective	CT-P13	CD-29, UC-11	Induction (12)	No
Kang et al. 2018 (52)	Prospective	CT-P13	CD-32, UC-6	Maintenance (52)	Yes
Choe et al. abstract (ECCO 2017, P487, S326)	Prospective	CT-P13	CD-26, UC-16	Induction and maintenance (30)	No
Chanchlani et al. 2018 (53)	Prospective	CT-P13	CD-63, UC-14, IBDU-5	Induction (12)	No
Muhammed et al. abstract (ECCO 2017, P382, S291)	Retrospective	CT-P13	CD-18, UC-6	Induction (14)	No
Wahid et al. abstract (ESPGHAN 2017, G-O-036)	Prospective	CT-P13	CD-60, UC-20	Induction (14)	No

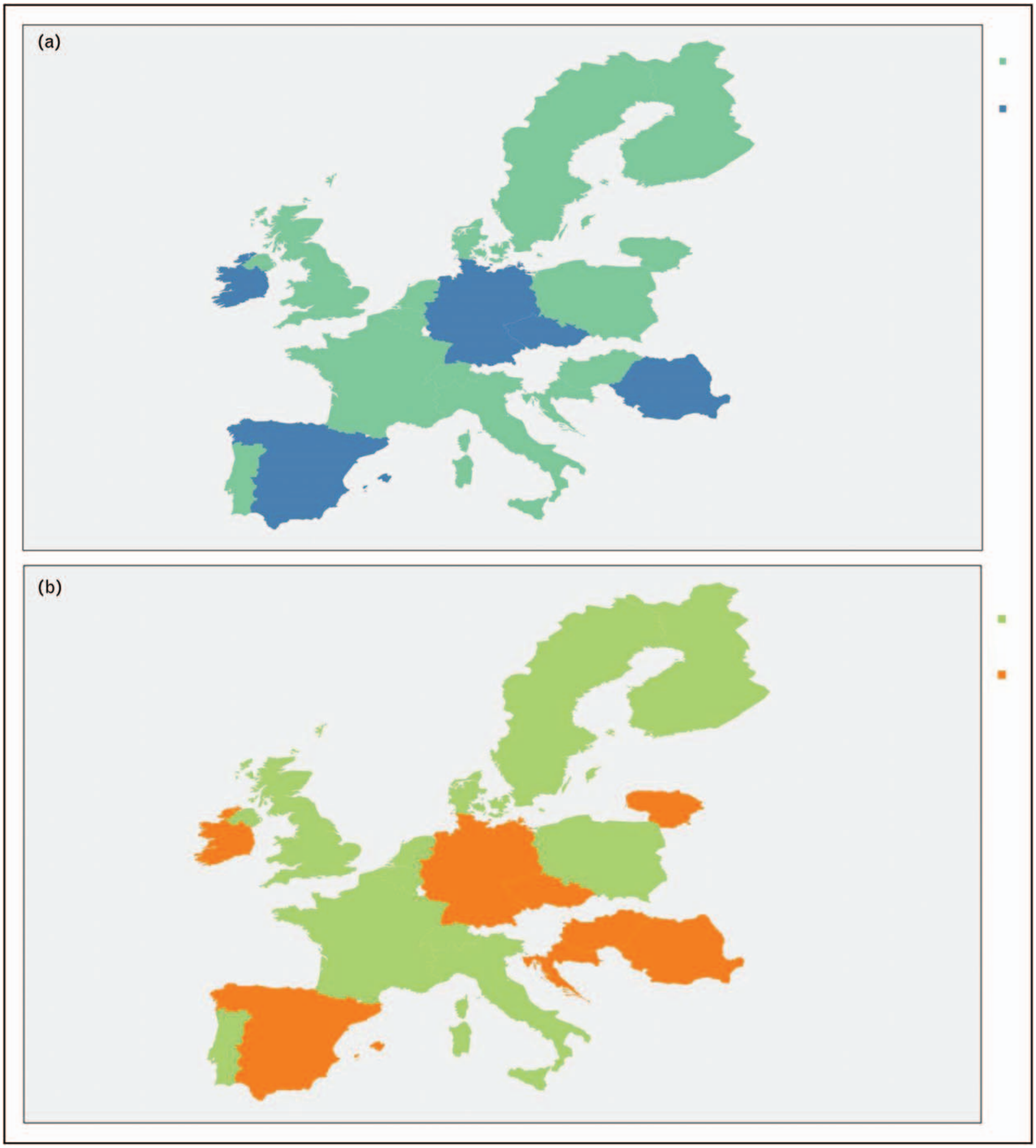

FIGURE 1. (A) European countries regularly prescribing CT-P13 (green countries). (B) European countries regularly switching to CT-P13 (green countries).

equivalent to IFX originator in term of efficacy, safety, and immunogenicity (56). In an extension phase of that study half of the patients were transitioned from originator infliximab to SB2 with excellent results (57).

Switching

In a prospective observational cohort study in 83 patients (57 CD, 24 UC, 2 IBD-U) (58), there was no change in disease activity, C-reactive protein, and fecal calprotectin 4 and 12 months (49) post-switching. IFX trough levels (TLs) remained stable with a median TL of 3.6 ng/mL at week 0 and of 3.7 ng/mL at week 52. ADAs were found in 8% of patients during follow-up but most of these had titers already detectable before switching. Six patients (7%) discontinued CT-P13 due to adverse events.

These results are in line with the recently published NOR-SWITCH study (34). This is the first, randomized double-blind non-inferiority trial on switching from originator IFX to BioS CT-P13 compared with maintenance treatment with originator across all indications (IBD and rheumatologic conditions) on stable treatment for at least 6 months. Of the overall 482 patients, 32% had CD and 19% had UC. Worsening of disease after 52 weeks occurred similarly in patients in both groups (26% in the originator group and 30% in the CT-P13 group). The 95% confidence interval was within the predefined non-inferiority margin of 15% in all disease subgroups, although the trial was not designed nor powered to demonstrate non-inferiority within each subgroup. TLs were similar in the 2 groups as well as the incidence of ADAs formation and adverse events.

The PROSIT-BIO—a prospective, multicenter cohort study (54) (547 IBD patients; 311 naïve, 139 previously exposed, 97 switched) demonstrated comparable efficacy (74%, 62%, and 79% at week 24 respectively) and incidence of adverse events following the switch.

In view of all the recent published studies the European Crohn's and Colitis Organization (ECCO) published an update (59) of the previous position statement (14) on the use of BioS in IBD stating that switching from the originator to a BioS in patients with IBD is acceptable, but evidence is lacking regarding reverse switching, multiple switching and cross switching. The authors also agreed that data on the usage of BioS may be extrapolated from other indications.

Immunogenicity

Immunogenicity of biologics primarily manifests as the formation of ADAs (neutralizing and non-neutralizing), which may be associated with adverse clinical outcomes, including altered pharmacokinetics (60), reductions of efficacy, (61–64) and allergic drug reactions (61–63). Neutralizing ADAs may diminish therapeutic activity by interfering with the drug ability to bind its target, while both neutralizing and non-neutralizing antibodies can impact the clinical response by forming immune complexes which may increase drug clearance thus lowering its serum concentration (65).

The immunogenicity of IFX is partially attributed to the murine component in the Fab fragment inducing the formation of human anti-chimeric antibodies (66). ADAs formation during IFX treatment was consistently shown to be associated with a loss of clinical response (67–69), and an increased rate of infusion reactions (70).

In vitro studies demonstrated that IFX derived antibodies tested against Remicade and CT-P13 yielded similar recognition patterns, indicating that both drugs have similar immunogenic structure (71). Additionally, ADAs from the sera of IFX-treated IBD patients recognized CT-P13 with almost perfect similarity (72). CT-P13 and SB2 were shown to cross-react with antibodies to reference IFX denoting that there are common immune dominant epitopes between IFX and CT-P13 or SB2 (72–76).

In healthy adult subjects who received a single infusion of either Remicade or SB2 IFX BioS, ADAs rate did not differ between groups after 10 weeks (77). In vivo immunogenicity of Remicade and its BioS CT-P13 was first assessed in 2 clinical trials in patients with RA (PLANETRA) and ankylosing spodilitis (PLANETAS), showing no differences in the incidence of ADAs between both drugs (52.3% and 49.5% at week 54 in the PLANETRA trial and 22.9% versus 26.7% in the PLANETAS trial for CT-P13 and Remicade, respectively) (21,23,78,79). Similarly, no significant difference in ADAs was observed in anti-TNF naïve IBD patients treated with either Remicade or CT-P13 and followed for 38 weeks (80).

Another pertinent issue is whether switching promotes an accelerated rate of ADAs formation. In the PLANETRA and PLANETAS extension trials, immunogenicity was comparable between the non-switched and switched groups at study end (81–83). In the recent NOR-SWITCH study, incidence of ADAs was similar for patients receiving reference IFX versus CT-P13 across all diseases (34). Kolar et al (84) reported no difference in ADA positivity at initiation and at week 24 of CT-P13 IBD-treated patients after switching from originator IFX (9.5% vs 10%, $P = 0.79$). In a recent study of 143 IBD patients who were switched from originator IFX to CT-P13, there was no increase in mean ADA levels after the switch (85).

A recent systematic review (86) including 616 IBD patients from 6 studies (283 switched and 333 non-switched) reported no significant difference in terms of immunogenicity between the originator IFX and its BioS CT-P13. In a single pediatric study, no increase in the immunogenicity was observed after switching to CT-P13 therapy (32). At the time of switching, 7 patients of 16 had positive ADA levels (>2 ng/mL) while after switching, only 4 patients have maintained ADA positivity. Comparable immunogenicity was confirmed in the most recent pediatric switch study (52).

As with IFX, immunogenicity to adalimumab is strongly linked to sub-therapeutic serum drug levels and a lack of clinical response (64). Several adalimumab BioSs are in development with emerging preclinical and clinical data including immunogenicity. The adalimumab BioS BI 695501 was compared with the reference agent in a randomized, double-blind, phase 1 clinical study (VOLTAIRE-PK, 327 healthy subjects) showing similar immunogenic response (87).

ABP-501, another adalimumab BioS, did not show any immunogenicity concerns in healthy adults (88). In 2 phase 3 double-blind randomized controlled clinical trials in patients with either plaque psoriasis (89,90) or RA (91,92) including switching from the originator adalimumab to either ABP 501 (psoriasis trial) or SB5 (RA trial), immunogenicity was not affected by switching treatments.

The effect of pre-medication before IFX infusion and of combination therapy with immunomodulators on ADAs formation in patients receiving originator IFX versus its BioS was not directly assessed in comparative studies. Nevertheless, indirect evidence from adults suggests that combination therapy of immunomodulators with CT-P13 diminishes ADAs formation similar to what is known for reference IFX (85).

Taken together, there is no evidence that immunogenicity differs between the originator IFX or adalimumab and their BioS, mostly based on adult studies. As immunogenicity of the originator biologic drugs was not shown to differ substantially between adults and children (93), it is reasonable to extrapolate the current adult data to the pediatric population.

Cost Effectiveness of Anti-Tumor Necrosis Factor Alpha Biosimilars

Over the past 15 years, biological drugs gained a significant share in the global drug market. It is projected, that by 2020 biologicals could account up to 28% of the global drug market (94). The relatively high cost of the reference biologics can be a limiting factor for patient access to these pharmaceuticals. With a more favorable pricing and reimbursement plan, BioS will raise the cost-utility of this therapeutic strategy, as BioS induced a 25% to 70% price reduction in Europe compared to the originator products (95).

In 2017, a critical review of the available budget impact analyses reported 12 non-overlapping budget analyses (3 were peer-reviewed full papers and 9 studies presented in a poster form) (96).

The first analysis from 2014 estimated the budget impact of BioS IFX in the indication of RA in 6 Central and Eastern European countries over a 3 year period (97).

The analysis of Jha et al. from 2015 projected 1-year cumulative cost savings for usage of BioS drugs in all autoimmune indications (including CD and UC) for 5 European countries (Belgium, Germany, Italy, Netherlands, UK). The estimated cumulative cost saving was substantial (with a 10%–30% price discount) (98,99).

The studies assessing the effect of BioS in economic considerations have made very conservative estimations of the economic benefits of 10% to 30% price discount which is likely to underestimate the financial impact of BioS, as it is suggested that price reduction could reach 60% to 70%. A detailed budget impact study for TNF-α inhibitor treatment in RA and IBD using 5 different scenarios in 5 large Western European countries demonstrated how switching policies discount rates changed drastically in 2 years time (100).

In summary, the available sources, based mostly on adult studies, strongly suggest that market introduction and reimbursement of less costly BioS will lead to considerable long-term budget savings, wider patient access, and therefore, improved patient outcomes.

Future Developments/New Biosimilars in the Pipeline

There are several BioSs for IFX and adalimumab, which already received approval from EMA (Table 1). However, there are many more BioSs in development. Currently, a total of ∼16 adalimumab and ∼6 IFX BioSs (not EMA/FDA approved) are evaluated in clinical trials. Most phase 3 trials of these new BioSs are still restricted to patients with RA, ankylosing spondylitis and psoriasis. This is because these disease models are more sensitive to illicit possible differences between innovator and biosimilar, in contrast to IBD which has a large inter- and intra-patient variability. Currently, only 1 phase 3 trial, comparing BioS BI 695501 with Humira is being performed in patients with active CD (101). Further efforts are underway to develop so called ''bio-betters,'' with better clinical profile than originators due to alteration of their chemical composition and formulation (86,102).

Although IFX and its BioS pharmacokinetic properties appear to be comparable between pediatric and adult patients with IBD, dosing needs can be higher in children compared to adults (103). Furthermore, future studies need to assess multiple switches from 1 BioS to another if this is becoming clinical practice and also back to the originator product (interchangeability) in both adults and children.

CONCLUSIONS

As more evidence regarding efficacy, immunogenicity, and interchangeability of BioS in IBD accumulates (thus increasing the level of confidence amongst clinicians and patients) it is likely that the utilization of BioS in IBD will grow leading to better availability for patients due to lower costs. The conglomerate of studies, predominantly head to head switching studies in IBD patients, increases the confidence that BioSs are indeed ''similar'' in their fundamental characteristics with no significant safety signals different from originator products. Nonetheless, each new BioS should be approached with some caution following scrutinized regulatory process and appropriate clinical data. Children, as a more vulnerable population with pharmacokinetic specificities (but not different from the originator products), should be addressed in future studies. It is mandatory to further standardize the regulatory legislation and clarify how interchangeability will be regulated in the future in order to permit efficient pharmacovigilance and help pharmacists and physicians. Until this has been solved it seems prudent to transition patients only on a long-term basis (arbitrarily 1 year or more) and to keep records of brands and batches that have been administered to patients, both for originator and biosmilar products.

Statements

1. There are sufficient data (by extrapolation from different indications, adult data and limited pediatric data) to state that in children with IBD who are indicated for IFX treatment, CT-P13 is a safe and efficacious alternative to the originator IFX for induction, and maintenance, of remission. 97% agreement
2. A switch from the originator IFX to CT-P13 may be considered in children with IBD in clinical remission, following at least 3 induction infusions. 84% agreement
3. Multiple switches (>1 switch) between various BioS or between BioS and the reference drug are not currently recommended in children with IBD, as data on interchangeability is still limited. Moreover, interchangeability compromises the traceability of the drugs in case of loss of efficacy and/or safety signals. 97% agreement
4. Sufficient post-marketing surveillance data on efficacy, safety, and immunogenicity in adult and paediatric patients with IBD should be a mandatory minimal requirement for the introduction of each new biosimilar for children with respective indications. For this, physicians/institutions should keep records of brands and batch numbers of all biological medicines administered. 89% agreement

DISCLAIMER

''ESPGHAN not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians''.

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